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HM12/1120

EXAMINER

GAMBEL, P

ART UNIT

PAPER NUMBER

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

## DETAILED ACTION

1. Applicant's amendment, filed 10/26/00 (Paper No. 5), is acknowledged.  
Claim 1 has been canceled. Claims 2-49 have been canceled previously.

Applicant's election of the species anti-CD28 antibodies in Paper No. 5, is acknowledged.

Accordingly, claims are withdrawn from consideration as being directed to a non-elected inventions/species. See 37 C.F.R. § 1.142(b) and M.P.E.P. § 821.03.

The instant claims, including claims 56 and 59, as they read on the second agent reading on "a stimulatory form of a natural ligand of CD28" (e.g. "B7-1") as the non-elected species from consideration under 37 CFR 1.142(b).

Claims 50-55, 57 and 58 are under consideration in the instant application.

2. The filing date of the instant claims is not readily apparent from a review of the priority application, as it is not readily apparent whether the priority applications, particularly the earliest priority applications, provide written description of the instant claims.

The written description of the instant claims, particularly

- (A) "a method for inducing ex vivo proliferation of a population of T cells";
- (B) "covalently attached thereto";
- C) "first and second agents";
- D) "a stimulatory form of a natural ligand of CD28 (e.g. B7-1)" ;
- E) "monitoring proliferation, reactivating and restimulating T cells"; and/or
- F) "the recitation of claim 58".

Since there may be ambiguity over the priority of the instant claims, rejections are made under 35 U.S.C. § 102(b), as it would apply to the priority of the instant claims.

If applicant can provide appropriate written support and enablement for the instant or possibly amended claims

Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

3. Applicant is reminded to amend the first line of the specification to update the status of priority documents

4. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84.  
Please see the enclosed form PTO-948.

The Brief Description of the Drawings should be amended to recite the different part numbers of the drawings (e.g. Figures 5A-C).

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 50-55 and 57 are rejected under 35 U.S.C. § 102(b) as being anticipated by Thompson et al. (WO 90/05541) (1449, #A3) (see entire document). Thompson et al. teach methods of immunotherapy by stimulating T cells with immobilized anti-CD3 antibodies and anti-CD28 (see Examples III-VIII). Also, Thompson et al. teaches such methods are desirable for enhancing T cell immune responses directed specifically towards T cells activated by antigen (page 1-2, overlapping paragraph). Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of the referenced methods.

8. Claims 50-55, 57 and 58 are rejected under 35 U.S.C. § 103 as being unpatentable over Weiss et al. (J. Immunol. 137: 819-825, 1986; 1449, #E2) AND/OR Ledbetter et al. (J. Immunol. 135: 2331-2336, 1985; 1449, #B12) in view of the art known use of covalently linking antibodies to solid phase to deliver stimulatory signals to cells of interest, including T cells as well as the art known practice to monitor cell proliferation of interest, including cell size and cell markers at the time the invention was made.

Weiss et al. teach stimulating proliferation in enriched T cells with immobilized anti-CD3 antibodies and saturating amounts of anti-Tp44 antibodies (i.e. anti-CD28) (see entire document; including Abstract, Results and Discussion)

Ledbetter et al. teach augmenting and sustaining the proliferation in mononuclear cell populations which comprise T cells with immobilized anti-CD3 antibodies and anti-Tp44 antibodies (i.e. anti-CD28) (see entire document; including Abstract, Results and Discussion). Weiss et al. teach that cross-linking of Tp44 molecules is required for stimulating T cells, given that Fab fragments of anti-Tp44 antibodies do not stimulate while F(ab')2 fragments (see Results and Discussion).

Weiss et al. And Ledbetter et al. differ from the claimed methods by not disclosing the art known use of immobilized anti-CD28 antibodies in combination of anti-CD3 antibodies per se in the stimulation of T cells of interest at the time the invention was made.

Given the art known use of applying immobilized antibodies to stimulate T cells, including the known use of anti-CD3 antibodies and multivalent forms /saturating amounts of anti-Tp44 (i.e. anti-CD28) antibodies to stimulate T cells, as taught by the teachings of Weiss et al. And Ledbetter et al.; one of ordinary skill in the art would have been motivated to stimulate antigen-specific T cells by covalently attaching both signals of anti-CD3 antibodies and anti-CD28 antibodies as a convenient and art known means to deliver said stimulatory signals to T cells ex vivo / in vitro. For example, it was known to provide such stimulatory signals by covalently linking the antibodies to plastic surfaces, as taught by Weiss et al. and Ledbetter et al. or via other convenient solid phase surfaces such as microbeads, as known and commercially available at the invention was made. It was readily understood and practiced by the ordinary artisan at the time the invention was made that by covalently linking such stimulatory agents to solid phase; the activated cells of interest would have been readily separated from the culture and agents and isolated accordingly.

Similarly, it was an art known practice to monitor cell proliferation of interest, including cell size and cell markers at the time the invention was made; as such criteria were known parameters of cell activation. Also, it was common practice at the time the invention was made to re-activate and re-stimulate cells to maintain proliferation and expansion of cell populations of interest at the time the invention was made.

Therefore, one of ordinary art at the time the invention was made would have expected to monitor the proliferation of said T cells by various parameters and to re-stimulate T cells undergoing expansion to achieve large number of cells of interest.

One of ordinary skill in the art at the time the invention was made would have been motivated to stimulate T cell activation with both CD3-/CD28-specific antibodies, including covalently linking both stimuli to solid phase surfaces, to increase T cell proliferation and numbers of T cells of interest for various purposes, such as T cell studies and adoptive immunotherapy. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary

9. Claims 50-55, 57 and 58 are rejected under 35 U.S.C. § 103 as being unpatentable over Weiss et al. (J. Immunol. 137: 619-625, 1986; 1449, #E2) AND/OR Ledbetter et al. (J. Immunol. 135: 2331-2336, 1985; 1449, #B12) in view of Zarling et al. (U.S. Patent No. 5,081,029)(~~1449~~)

Weiss et al. And Ledbetter et al. Are taught above in Section 8.  
Zarling et al. is set forth herein to provide the known motivation to stimulate and grow large number of T cells at the time the invention was made.

Zarling et al. teach methods of adoptive immunotherapy for treating various disorders, including stimulating antigen-specific T cells comprising CD3<sup>+</sup> T cells, including the use various stimuli including anti-Tp44 antibodies (column 7, paragraphs 1-2) for the expansion of t cells for adoptive immunotherapy(see entire document, including Summary of the Invention, Detailed Description of the Invention, Isolation, Activation and Expansion of Lymphocytes, including Examples).

Therefore, one of ordinary art at the time the invention was made would have expected to monitor the proliferation of said antigen-specific T cells , to re-stimulate T cells undergoing expansion to achieve large number of cells (e.g. 100-100,000-fold) required for adoptive immunotherapy.

One of ordinary skill in the art at the time the invention was made would have been motivated to stimulate T cell activation with both CD3-/CD28-specific antibodies, including covalently linking both stimuli to solid phase surfaces, to increase T cell proliferation and numbers of T cells of interest for various purposes, such as T cell studies and adoptive immunotherapy. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary

10. Claims 50-55, 57 and 58 are rejected under 35 U.S.C. § 103 as being unpatentable Thompson et al. (WO 90/05541) (1449, #A3 )in view of the art known use of covalently linking antibodies to solid phase to deliver stimulatory signals to cells of interest, including T cells as well as the art known practice to monitor cell proliferation of interest, including cell size and cell markers at the time the invention was made.

Thompson et al. teach methods of immunotherapy by stimulating T cells with immobilized anti-CD3 antibodies and anti-CD28 (see Examples III-VIII). Also, Thompson et al. teaches such methods are desirable for enhancing T cell immune responses directed specifically towards T cells activated by antigen (see entire document, including page 1-2, overlapping paragraph).

Thompson et al. differs from the claimed methods by not explicitly teaching covalently linking anti-CD28 antibodies per se and the monitoring of stimulated T cell populations by the claimed limitations per se.

However, it is noted that Thompson et al. Clearly teach monitoring various markers of activation (see entire document, including Examples).

Given the art known use of applying immobilized antibodies to stimulate T cells, including the known use of anti-CD3 antibodies and multivalent forms of anti-Tp44 (i.e. anti-CD28) antibodies to stimulate T cells, as taught by the teachings of Thompson et.; one of ordinary skill in the art would have been motivated to stimulate antigen-specific T cells by covalently attaching both signals of anti-CD3 antibodies and anti-CD28 antibodies as a convenient and art known means to deliver said stimulatory signals to T cells ex vivo / in vitro. For example, it was known to provide such stimulatory signals by covalently linking the antibodies to plastic surfaces, as taught by Weiss et al. and Ledbetter et al. or via other convenient solid phase surfaces such as microbeads, as known and commercially available at the invention was made. It was readily understood and practiced by the ordinary artisan at the time the invention was made that by covalently linking such stimulatory agents to solid phase; the activated cells of interest would have been readily separated from the culture and agents and isolated accordingly.

It was an art known practice to monitor cell proliferation of interest, including cell size and cell markers at the time the invention was made; as such criteria were known parameters of cell activation.

Also, it was common practice at the time the invention was made to re-activate and re-stimulate cells to maintain proliferation and expansion of cell populations of interest at the time the invention was made.

Therefore, one of ordinary art at the time the invention was made would have expected to monitor the proliferation of said T cells by various parameters and to re-stimulate T cells undergoing expansion to achieve large number of cells of interest.

One of ordinary skill in the art at the time the invention was made would have been motivated to stimulate T cell activation with both CD3-CD28-specific antibodies, including covalently linking both stimuli to solid phase surfaces, to increase T cell proliferation and numbers of T cells of interest for various purposes, such as T cell studies and adoptive immunotherapy. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

11. The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and © may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 50-55, 57 and 58 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over  
(claims 52, 62, 65, 80, 81, 84, 86, 88, 90, 92, 94, 95, 98, 99 and 102) of commonly assigned copending USSN 08/403,253 and  
(claims 1, 46, 47, 50, 51, 52, 56-58 and 71) of commonly assigned copending USSN 09/183,055.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant and copending claims appear to rely upon the same or nearly the same method steps and ingredients, particularly the use of anti-CD3 and anti-CD28 antibodies to stimulate and expand T cells, including CD8+ T cells.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claims 50-55, 57 and 58 are directed to an invention not patentably distinct from  
(claims 52, 62, 65, 80, 81, 84, 86, 88, 90, 92, 94, 95, 98, 99 and 102) of commonly assigned copending USSN 08/403,253 and  
(claims 1, 46, 47, 50, 51, 52, 56-58 and 71) of commonly assigned copending USSN 09/183,055.  
for the reasons set forth above in Section 12.

Commonly assigned USSN 08/403,253 and USSN 09/183,055; discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. § 103 if the commonly assigned case qualifies as prior art under 35 U.S.C. § 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 C.F.R. § 1.78© to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application. A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. § 103 based upon the commonly assigned case as a reference under 35 U.S.C. § 102(f) or (g).

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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November 20, 2000